Estimation of Safe and Adequate Daily Intake for Arsenic*

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Arsenic (As) is generally found at low concentrations in drinking water (1–2 μg/L). In some areas, however, concentrations of 50–400 μg As/L of drinking water are found. Average daily dietary intake of arsenic by humans ranges from 12 to 40 μg. Seafood, grains, and cereal products contribute the most arsenic to the diet. Generally, the arsenic in water is inorganic and that of seafood is organic. Inorganic forms of arsenic are the most toxic; thus, when drinking water levels of arsenic are high, health problems may occur. Absorption of arsenic depends on the form and solubility of the arsenic compound: inorganic arsenic is methylated in the liver. If arsenic ingestion is low, accumulation is not significant in any tissue; however, the highest concentrations of arsenic are usually in the skin, hair, and nails. Arsenic is excreted rapidly, usually in urine. Studies with rats, hamsters, chicks, goats, and minipigs have provided evidence supporting the essentiality of arsenic; thus, it is likely arsenic will be found to be essential for humans. An arsenic requirement between 25 ng and 50 ng/g diet was suggested for growing rats and chicks eating a diet containing approximately 4000 kcal/kg. Based on this, a calculated arsenic requirement for humans eating 2000 kcal would be 12–25 μg/day.

Dietary Sources

In a 24-hour duplicate diet study, Dabeka et al. (1987) found a mean dietary intake of 16.7 μg/day for a group of adults living in five Canadian cities. Food items were broken down into 10 categories. Mean arsenic concentrations ranged from 0.46 ng/g for drinking water to 60.1 ng/g for meats and fish. The food categories contributing most of the arsenic to the diet were cereals and breads (18.1%), starch vegetables (14.9%), and meats and fish (32.1%). Arsenic is generally high in seafood (e.g., clams, 2.3 μg/g; salmon, 1 μg/g; and tuna, 0.39 μg/g). Thus, eating a disproportionate amount of seafood can drastically alter daily arsenic intake. Arsenic concentrations on a dry weight basis

*Editor's comment: It is important to note that at the present time, arsenic is not recognized as an essential element in humans.

(μg/g) of selected food items are wheat flour, 0.01–0.09; rice, 0.4; carrots, 0.03–0.8; potatoes, 0.01–0.02; and apples, 0.04–1.72. Arsenic concentrations on a fresh weight basis (μg/g) of selected food items are chicken, 0.02; shrimp, 1.3–42; milk, 0.0005–0.07; and cod, 2.2 (National Academy of Science [NAS] 1977). Other studies report daily arsenic intakes of 12 to 40 μg/day (Buchet et al. 1983, Mykkänen et al. 1986, Evans and Sherlock 1987). The FAO/WHO maximum acceptable daily load of arsenic for humans is 2 μg/kg (Dabeka et al. 1987).

Metabolism

Inorganic arsenate or arsenite is readily absorbed (>90%) if the ingested inorganic arsenic is soluble. Organic arsenic from seafood is also highly absorbed (about 80%); other organic arsenic compounds are only 15–40% absorbed (Ishinishi et al. 1986). Both inorganic arsenite and arsenate (following reduction to arsenite) are methylated in the liver, and the enzymatic reaction requires glutathione and S-adenosylmethionine (Buchet and Lauwerys 1988). Oxidation of arsenite to arsenate can also occur (Vahter and Envall 1983). Excretion of arsenic is mainly through the urine; the rate of urinary excretion depends on the form of arsenic ingested, with only a few percent of the ingested arsenic excreted in the feces (Bertolero et al. 1981, Mealey et al. 1959). In humans, the urinary excretion of a low oral dose of inorganic arsenic consists of approximately 20% inorganic arsenic, 20% monomethylarsonic acid, and 60% dimethylarsinic acid (Crecelius 1977, Tam et al. 1979, Buchet et al. 1981a). A trimethyl form of arsenic has also been reported in the urine following exposure to seafood arsenic (Yamato 1988). In humans there apparently are three phases of urinary excretion of arsenic: after intravenous injection of arsenite the biological half-lives of pools were determined to be 2, 8, and 192 hours (Mealey et al. 1959), after oral ingestion of arsenate, 66% of the dose was eliminated with a half-life of 2.1 days, 30% of the dose with a half-life of 9.5 days, and 3.7% of the dose with a half-life of 38 days (Pomroy et al. 1980). After organic arsenic ingestion from seafood, the half-life was estimated to be less than 20 hours (Ishinishi et al. 1986).

Excessive Intakes and Toxicity

Because of the mechanisms for homeostatic regulation, the toxicity through oral intake of arsenic is relatively low. Valentine et al. (1979) found that it was necessary to consume at least 200 μg As per day before blood arsenic concentrations increased. Vallee et al. (1960) estimated that the acute fatal dose of arsenic trioxide for humans is 70–180 mg. It has been calculated that there is more than a 1000-fold difference between the ratio of acute arsenic toxicity to nutritional

dose for rats (Nielsen and Uthus 1984). Also, no adverse effects were seen in rats supplemented with 5 μg As (as sodium arsenite)/mL in their drinking water from weanling to death (Schroeder et al. 1968). Thus, there is at least a 100-fold difference between a chronic toxic dose of arsenic and the required amount of arsenic for the rat. In humans, there is a slightly reduced methylation capacity above 250 μg As/day (Buchet et al. 1981b). Thus, assuming 100% absorption and diets supplying 12–40 μg As/day, normal daily intake and lowest observed effect on arsenic methylation capacity ranges from a factor of 6 to a factor of 20. These ratios are probably low because arsenic from food is absorbed at less than 100%, probably closer to 80%. Organic arsenic is virtually nontoxic. A 10-g dose of arsenobetaine per kilogram body weight depressed spontaneous mobility and respiration in male mice, but these symptoms disappeared within an hour (Kaise et al. 1985).

The signs of subacute and chronic exposure to high concentrations of arsenic in humans include the development of dermatoses of various types, hematopoietic depression, liver damage, sensory disturbances, peripheral neuritis, anorexia, and loss of weight (Ishinishi et al. 1986). Numerous epidemiologic studies have suggested an association between chronic high arsenic exposure and cancer. The role of arsenic in the carcinogenesis process, however, remains controversial. Arsenic is a clastogen, and recent evidence suggests that it is not a primary carcinogen or initiator but may be a cocarcinogen, promoter, or a copromoter (Brown and Chu 1986, Fowle et al. 1991).

Essentiality Studies

Early attempts to prove the essentiality of arsenic were unsuccessful or had confusing results because the arsenic content in the arsenic-deficient diets was unknown or too high, or because the arsenic content of the control diets was too high. The results of several studies also were confounded by the use of diets that were nutritionally incomplete and thus contributed to the poor growth of the control animals.

The first strong evidence of arsenic essentiality were provided by studies by Nielsen et al. (1975) and Anke et al. (1976). In the studies by Nielsen and coworkers (1975), rats were fed a diet based on skim milk and acid-washed corn. The basal diet contained approximately 30 ng As/g; control diets were supplemented with 4.5 μg As/g. Dams were placed on the diet within 2 days of being bred. The offspring of the arsenic-deprived dams displayed a rougher coat and a slower growth rate than the offspring from the controls. Males were more affected than females by arsenic deprivation. At 12–15 weeks after birth, the

arsenic-deprived males, compared to controls, exhibited enlarged blackened spleens containing 50% more iron on a per gram basis. The spleens of the arsenic-deprived females were also enlarged but to a lesser extent than the spleens from males. In both sexes, arsenic deprivation caused an elevated erythrocyte osmotic fragility.

Anke et al. (1976) presented evidence for the essentiality of arsenic for goats and minipigs. A semisynthetic diet containing less than 50 ng As/g was fed to growing, pregnant, and lactating goats and minipigs, and to first- and second-generation offspring. Controls received 350 ng As/g diet. Only 58% of the arsenic-deprived goats and 62% of the arsenic-deprived minipigs produced offspring compared to 92% and 100% of the respective controls. The offspring from the arsenic-deprived animals exhibited depressed growth and elevated mortality rate. Some lactating arsenic-deprived goats died, apparently from myocardial abnormalities. There was an increase in mitochondrial membrane contour ultrastructurally in the heart; a fine granular and electron dense material was also seen in the membrane. At a more advanced stage, a rupture of the mitochondrial membrane occurred (Anke 1986).

Nielsen and Shuler (1978) reported findings of essentiality for arsenic in growing chicks. Day-old cockerel chicks were fed a diet based on dried skim milk, acid-washed corn, and high-protein casein. The basal diet contained approximately 15–25 ng As/g. Controls received the basal diet supplemented with 1 μg As/g. Some of the arsenic-deprived and arsenic-supplemented chicks were supplemented with 20 g arginine/kg diet. After 4 weeks the arginine-supplemented, arsenic-deprived chicks weighed significantly less than comparable controls. Other findings of arsenic deprivation in the arginine-supplemented chicks included an elevated liver weight/body weight ratio and an elevated concentration of zinc and depressed concentrations of arsenic, iron, and manganese in the liver. In retrospect, the study by Nielsen and Shuler (1978) was the first performed in which arsenic deprivation was studied in animals with a stressed methionine metabolism. Guanidoacetate, formed in the metabolism of arginine, is methylated by S-adenosylmethionine forming creatinine. Thus, feeding high amounts of arginine can result in an induced methyl/methionine deficiency because of the required methylation in the metabolism of guanidoacetate. Shortly after the study of Nielsen and Shuler (1978), experiments in the laboratories of Nielsen and Uthus focused on ascertaining the possible physiologic importance of arsenic in methionine metabolism.

The effects on arsenic deprivation of methyl depletion as the result of high dietary guanidoacetate (GAA) were studied in rats and chicks (Uthus and Nielsen 1986). Day-old cockerel chicks were assigned to

groups of similar weight in a fully crossed, three-factor design. The dietary variables were arsenic, 0 or 2 μg/g; choline, 0.65 or 1.3 g/kg; and GAA, 0 or 5 g/kg. The basal diet contained about 15 ng As/g. After 28 days, an interaction between arsenic and GAA affected body weight, hemoglobin, and plasma total creatine-creatinine. Regardless of dietary choline, GAA markedly depressed growth and hemoglobin concentration; arsenic deprivation exacerbated the depression. GAA supplementation elevated plasma total creatine-creatinine; arsenic deprivation enhanced this elevation. In experiments with rats, GAA was supplemented at 5 g/kg diet, and choline, folic acid, and vitamin B_{12} were all excluded from the diet (Uthus and Nielsen 1987). In the chick and the rat experiments, arsenic deprivation depressed growth.

In a study by Cornatzer et al. (1983), the effect of arsenic deprivation on phosphatidylcholine biosynthesis in liver microsomes of the rat was determined. At 71 days of age, compared to controls fed 2 μg As/g, male rats fed a diet containing less than 15 ng As/g had a depressed specific activity of phosphatidylethanolamine methyltransferase and depressed total liver microsomal activities of phosphatidylethanolamine methyltransferase, phosphatidyldimethylethanolamine methyltransferase, and choline phosphotransferase.

The studies described above demonstrate that the nature and severity of the signs of arsenic deprivation are affected by dietary manipulations that impact methionine metabolism, and that many signs of arsenic deprivation include apparent perturbations in methionine metabolism. Because S-adenosylmethionine is of dominant importance in the metabolism of methionine, and because it is involved in polyamine biosynthesis, an experiment was performed to determine the effect of arsenic deprivation on polyamine biosynthesis (Uthus et al. 1989). Arsenic deprivation decreased spermidine to 89% and spermine to 90% (on a per gram basis) of respective control values. S-adenosylmethionine decarboxylase was decreased to 83% of the control value by arsenic deprivation; ornithine decarboxylase tended to be decreased by arsenic deprivation.

In a 2 × 2 factorially arranged experiment, an amino acid-based diet was utilized to ascertain the effects of a simple dietary methionine deficiency on arsenic deprivation (Uthus and Poellot 1990). Dietary variables were methionine, 1 or 5 g/kg, and arsenic, 0 or 1 μg/g. The basal diet contained 0.14% methionine and about 10 ng As/g. Arsenic deprivation decreased growth and mean corpuscular hemoglobin in rats fed 1 g methionine/kg diet but had no effect on those variables in rats fed 5 g methionine/kg diet; this resulted in a significant interaction between arsenic and methionine. An interaction between arsenic and methionine also affected mean corpuscular volume, bone concentrations

of copper, potassium, magnesium, and zinc, and heart concentration of calcium. Also, bone, heart, and plasma iron concentrations tended to be increased by arsenic deprivation in the rats fed 1 g methionine/kg diet.

Several of the findings from the above experiment were similar to signs of vitamin B_6 deficiency. Other studies have also produced findings that signs of arsenic deprivation are similar to signs of vitamin B_6 deficiency. These include a decrease in the specific activity of liver cystathionase and a tendency for a decrease in the specific activity of ornithine decarboxylase (both enzymes utilize the cofactor pyridoxal phosphate); a decrease in rat and hamster plasma taurine (taurine synthesis requires vitamin B_6); and changes in mean corpuscular volume, mean corpuscular hemoglobin, total blood hemoglobin, hematocrit, and tissue iron (all of which can be affected by changes in vitamin B_6 metabolism). Therefore, a $2 \times 2 \times 2$ experiment was designed to ascertain the effect of pyridoxine on arsenic deprivation in rats (Uthus and Poellot, in press). Dietary variables were arsenic, 0 or 1 μg/g, methionine, 0 or 3 g/kg, and pyridoxine, 0 or 10 mg/kg. The basal diet contained less than 15 ng As/g and 0.24% methionine.

After 10 weeks, growth was reduced by arsenic, pyridoxine, or methionine deprivation. Both endogenous (-PP) and pyridoxal 5′-phosphate (+PP) erythrocyte aspartate aminotransferase were decreased by pyridoxine deficiency. The ratio of +PP/-PP, known as the activation coefficient (AC), was affected by an interaction between arsenic and pyridoxine. Pyridoxine deficiency resulted in a less-marked increase in AC in the arsenic-deprived rats than in the arsenic-supplemented rats. The iron concentration in plasma was slightly decreased by pyridoxine deficiency in the arsenic-deprived rats but increased by pyridoxine deficiency in the arsenic-supplemented rats. Plasma threonine and serine were increased by arsenic supplementation in the pyridoxine-deficient rats but there was no effect of arsenic supplementation on these amino acids in the pyridoxine-supplemented rats. The concentration of alanine in plasma was decreased by arsenic or pyridoxine deprivation. In pyridoxine deficiency, arsenic deprivation had no effect on plasma glycine concentration in the methionine-deficient rats but decreased the concentration of plasma glycine in the methionine-supplemented rats. In the pyridoxine-supplemented rats, arsenic had no effect on plasma glycine concentration, regardless of dietary methionine.

Possible Site of Action or Physiologic Role of Arsenic

The signs of arsenic deprivation are numerous and have been described for the goat, minipig, rat, hamster, and chick. The responses to arsenic deprivation have varied in nature and severity with alteration in

dietary concentrations of numerous substances, including arginine, choline, guanidoacetate, pyridoxine, and methionine. These substances are all related because they affect methionine metabolism.

There are several areas in methionine metabolism in which arsenic could have a physiologic role. The areas under consideration involve the biosynthesis and metabolism of taurine and the polyamines and the metabolism of labile methyl groups from methionine.

Estimated Safe and Adequate Daily Dietary Intake

Presently there is not an accurate measure for assessment of arsenic status in humans or laboratory animals, and there is not any conclusive evidence of human arsenic essentiality. A report by Mayer et al. (1993) correlates low serum arsenic concentrations in hemodialysis patients with central nervous system disorders, vascular diseases, and cancer. Mean serum arsenic concentration in the hemodialysis patients was 8.5 ± 1.8 ng/mL; in controls the concentration was 10.6 ± 1.3 ng/mL. The authors concluded that arsenic homeostasis was altered by hemodialysis treatment and certain diseases and, therefore, maintaining desirable arsenic concentrations in the body seemed reasonable. Furthermore, the authors suggested that arsenic deficiency may impose an additional risk to hemodialysis patients and that supplementation may be appropriate. These may be the first reported cases of arsenic deficiency in humans. Also, pathological conditions in humans have not been attributed to arsenic deprivation. Thus, any estimated safe and adequate daily dietary intake (ESADDI) must be extrapolated from animal findings but balance studies have not yet been undertaken to determine the requirement of arsenic for laboratory animals. There have been, however, several studies that determined the response of arsenic deprivation signs in rats and chicks to graded amounts of supplementary arsenic. In experiments done by Uthus et al. (1983), an arsenic requirement of less than 50 ng/g diet, and probably near 25 ng/g diet, was suggested for growing chicks and rats fed experimental diets containing about 20% protein, 9% fat, 60% carbohydrate, and 11% fiber, minerals, and vitamins. Thus, these diets contained approximately 4000 kcal/kg. Therefore, a possible arsenic requirement for humans eating 2000 kcal would be about 12–25 μg daily. In another study by Uthus (unpublished findings), four groups of chicks were fed a basal diet containing about 10 ng As/g. Arsenite, as $NaAsO_2$, was supplemented to the diet at 0, 0.1, 1, and 10 μg/g. The study indicated that 0.1 μg As/g of diet was adequate and that the minimum requirement of arsenic for chicks fed an 18% casein, 67% ground corn, and 7.5% corn oil diet is between 0.01 and 0.1 μg As/g diet. Without further information on how the chicks would have responded in this

study to supplements lower than 0.1 μg/g diet, a minimum requirement of the chick for arsenic is still assumed to be 25–50 ng/g.

Given the apparent lack of arsenic deficiency as a practical nutritional problem in humans and the derived requirement of arsenic for humans, it would seem that current dietary intakes satisfy the needs for arsenic. Thus, it seems appropriate to suggest that an ESADDI of arsenic by adults is 12–40 μg. By extrapolation on a body weight basis and an arsenic ESADDI of 12–40 μg for a 70 kg person, the arsenic ESADDI for infants 0–0.5 years (6 kg) is 1–4 μg; infants 0.5–1 years (9 kg), 2–5 μg; children 1–3 years (13 kg), 3–8 μg; children 4–6 years (20 kg), 4–12 μg; and for children 7–10 years (28 kg), 5–16 μg. The upper limit of the safe and adequate range probably could be higher than 140 μg/day because arsenic apparently is not toxic at intakes between 140 and 250 μg/day. This statement is based on FAO/WHO maximum acceptable daily load for a 70-kg person (Dabeka et al. 1987) and a study by Buchet et al. (1981b) that showed that the methylation capacity of humans was only slightly reduced when oral intakes exceeded 250 μg As/day. Until more precise recommendations can be made, the consumption of a well-balanced and varied diet is the best assurance of a safe and adequate intake of arsenic based on extrapolated values of arsenic requirements for humans (12–25 μg daily) and on the average daily intake of arsenic by humans (12–40 μg/day).

An element is considered essential when a deficiency of the element produces an impaired function that can be overcome by supplementation of physiologic amounts of the element. Ultimately, the biochemical basis for essentiality must be demonstrated. Because the postulated dietary requirement for humans (12–25 μg daily) is close to the average daily intake of arsenic (12–40 μg), an inadequate intake of arsenic detrimental to optimal health and well-being could possibly occur. This possibility could be enhanced by other conditions. As adapted from Nielsen (1991) for trace and ultratrace elements in general, these conditions include 1) inborn errors of metabolism that affect absorption, retention, or excretion; 2) alterations in metabolism or biochemistry as a secondary consequence to malnutrition, disease, injury, or stress; 3) omission from a total parenteral nutrition solution; 4) marginal deficiency induced by various dietary manipulations or by antagonizing interactions with other nutrients or drugs; and 5) the enhanced requirement for a trace element caused by a sudden or severe change in the system requiring that element. Thus, the closeness of the postulated requirement and reported average intake of arsenic may be of concern, especially if the need for arsenic is enhanced by nutritional stressors that upset sulfur amino acid or labile methyl metabolism.

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